Use of enoxaparin in patients with heparin-induced thrombocytopenia syndrome

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Purpose: To determine whether low molecular weight heparin (LMWH) can be an alternative to unfractionated heparin (UH) for patients with heparin-induced thrombocytopenia syndrome (HIT).

Methods: The diagnosis of HIT was established in 126 patients by platelet aggregometry with UH (1 U/ml). These plasma samples were also tested for the ability to aggregate platelets in the presence of the LMWH enoxaparin (1 U/ml). Two patients with the HIT syndrome, after negative platelet aggregometry testing with enoxaparin, were anticoagulated with enoxaparin.

Results: Fifteen plasma samples that tested negative to UH also tested negative to enoxaparin. Forty-three of 126 (34%) UH-positive plasma samples aggregated platelets in the presence of enoxaparin. Twenty-two of 102 (22%) plasma samples with limited positive aggregation responses (minimal or no change in optical density) aggregated platelets in the presence of enoxaparin. However, 21 of 24 (88%) strongly positive plasma samples (30% to 60% change in optical density at 3 to 27 minutes) also aggregated platelets in the presence of enoxaparin. Two patients with HIT who received enoxaparin after aggregation testing demonstrated no cross-reactivity to enoxaparin achieved adequate anticoagulation and did not develop HIT.

Conclusions: Thirty-four percent of plasma samples from patients with HIT (88% of those strongly positive) aggregated platelets in the presence of enoxaparin. Patients with HIT may safely receive enoxaparin if their plasma does not aggregate platelets in the presence of enoxaparin. (J Vasc Surg 1996;23:839-43.)

Heparin-induced thrombocytopenia (HIT) is a dose-independent reaction to heparin that is caused by heparin-associated antiplatelet antibodies (HAAb) and occurs in 2% to 4% of patients receiving heparin. The thrombocytopenia usually occurs 5 to 14 days after initiation of heparin therapy but may occur immediately upon re-exposure to heparin. HIT is associated with thromboembolic complications in 22% to 61% of patients[1,2] and with hemorrhagic complications in 5% of patients.[3]

Because heparin is used so frequently, a large number of patients will develop heparin-associated antiplatelet antibodies. It is accepted that anticoagulation with heparin should be avoided in patients with HIT; however, these patients commonly have illnesses that require continued anticoagulation with an agent that may be rapidly titrated to effect. This need has prompted the search for alternatives to unfractionated heparin (UH) in patients with HIT.

When low molecular weight heparins (LMWHs) and heparinoids were introduced, it was believed that they would have application as a substitute for UH in patients with HIT; however, clinical studies have produced conflicting results. Some investigators report resolution of thrombocytopenia,[4-12] whereas others report persistent thrombocytopenia.[13-16] Previously published data from our laboratory revealed that the LMWHs mono-embolex NM and fragmin and the heparinoid Org 10172 have the ability to aggregate platelets (60.8%, 25.5%, and 19.6%, respectively) in the presence of HAAb.[17] This study evaluated the ability of enoxaparin to aggregate platelets in the presence of HAAb and the value of enoxaparin in managing patients with HIT.

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METHODS

From November 1993 through March 1995, all plasma samples from patients suspected of having HIT that aggregated platelets in the presence of beef or pork heparin were also tested with enoxaparin. The first 15 plasma samples that did not aggregate platelets in the presence of UH were also tested with enoxaparin. HIT was suspected in patients receiving any form of UH when at least one of the following was present: platelet count <100,000 mm^3 or substantial decrease (>15%) in the platelet count during heparin administration, resistance to anticoagulation with heparin, or thrombohemorrhagic event(s) while receiving heparin.

This study was approved by the Institutional Review Board of the University of Missouri Hospital and Clinics.

Our method for platelet aggregometry has been reported in detail.[18] Platelet rich plasma (PRP, 0.16 ml) from an unaffected donor was combined with platelet-poor plasma (PPP, 0.24 ml) from the patient. UH (1 U/ml) was added to this plasma. Platelet aggregation was detected with a platelet aggregometer (Chronolog Corp., Haverton, Penn.) and confirmed by visual inspection.

Adenosine diphosphate, a potent stimulator of platelet aggregation, was used to confirm the ability of the donor platelets to aggregate. Incubations of PRP and saline, PRP and heparin, and PPP and saline were performed to rule out nonspecific aggregation. False-positive results were ruled out by placing the patient's PPP, normal PRP, and a higher concentration of heparin (100 U/ml) in the aggregometer. Aggregation occurring in the presence of a higher heparin concentration indicated a false-positive result.[19]

A positive result was assigned only when appropriate responses were present in all controls and platelet aggregation was seen when test PPP, normal PRP, and low-dose heparin were combined. The positive aggregation responses were subclassified into weak-positive and strong-positive on the basis of the following criteria: a weak aggregation response was assigned to those specimens with distinct aggregation visually noted after 27 minutes of incubation and minimal or no change in optical density; strong aggregation responses were characterized by aggregation before 27 minutes of incubation and a 30% to 60% increase in optical density. All plasmas with a positive aggregation response to UH were also tested with enoxaparin in the aggregometer.

Two patients with the HIT syndrome who tested negative for enoxaparin and who required further anticoagulation received enoxaparin.

RESULTS

Between November 1993 and March 1995, 126 patients (94 men, 32 women) with HAAb were identified with platelet aggregometry. Twenty-three plasma samples were referred to our lab for testing, and 103 were from patients in our health science center. Of the 126 plasma samples testing positive for HAAb, 43 (34%) also aggregated platelets in the presence of enoxaparin. 102 of 126 samples were graded as weak positives; only 22 (22%) of these aggregated platelets in the presence of enoxaparin. The remaining 24 samples had a strong platelet aggregation response to UH; 21 (88%) of these aggregated platelets in the presence of enoxaparin. The 15 plasma samples that tested negative to UH also tested negative to enoxaparin (Fig. 1).

During the study period, two patients with the HIT syndrome clinically required further anticoagulation. Each had a weak-positive aggregation response in the presence of UH, and neither aggregated platelets in the presence of enoxaparin.

The first patient was a 69-year-old white man who underwent emergent repair of a ruptured abdominal aortic aneurysm. His postoperative course was complicated by acute renal failure requiring hemodialysis. On admission, his platelet count was 165,000 mm^3. While receiving heparin for hemodialysis, his platelet count fell to 46,000 mm^3. On postoperative day 10, HAAb were documented by platelet aggregometry by UH. Enoxaparin did not induce platelet aggregation when combined with donor platelets and the patient's plasma; it was therefore used as an anticoagulant for hemodialysis. Platelet counts increased after institution of enoxaparin therapy to a high of 303,000 mm^3 (range 136,000 mm^3 to 303,000 mm^3). He received enoxaparin three times per week during hemodialysis until he died from adult respiratory distress syndrome and multisystem organ failure on postoperative day 54. No further thrombocytopenia or thrombohemmorhagic complications were noted.

The second patient was an 80-year-old white man who had severe abdominal pain, hypotension, and abdominal distention. His platelet count at the time of admission was 192,000 mm^3. Emergent laparotomy revealed a large retroperitoneal hematoma with active bleeding posterior to the body of the pancreas. No visceral aneurysms or other bleeding sites were encountered. An intracardiac thrombus was postoperatively documented by echocardiography and treated with UH. Several days after institution of UH therapy, his platelet count had fallen to 82,000 mm^3 and HAAb were documented by platelet aggregometry. Enoxaparin did not induce platelet

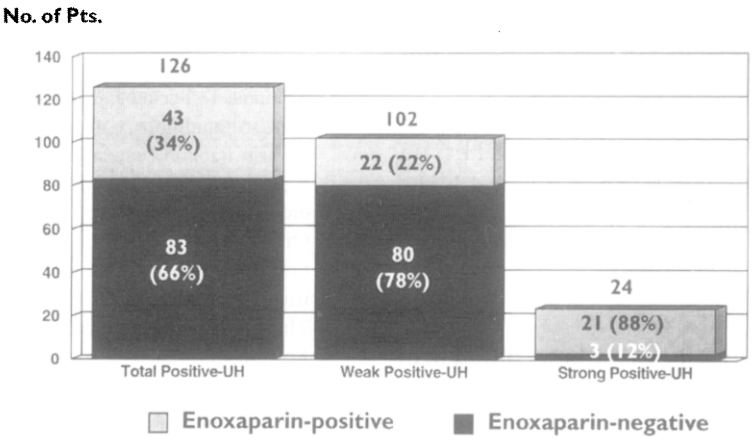

Fig. 1. Enoxaparin cross-reactivity in patients with heparin-induced thrombocytopenia syndrome.

aggregation; therefore, during the 2 weeks it was used for management of the mural thrombus, no further thrombocytopenia or thromboembolic sequelae were noted.

DISCUSSION

HIT, described in 1973,[20] has been recognized as a specific immune-mediated syndrome in which antiplatelet antibodies are generated in the presence of heparin. HIT occurs in 2% to 4% of patients exposed to any amount of heparin delivered by any route. The syndrome may occur in the presence of very small amounts of heparin (one unit per hour); even heparin-coated venous catheters have been implicated as causative agents in this syndrome.[3] Patients of any age are at risk for developing HAAb; the syndrome has been documented in infants.[21] HAAb may develop regardless of the type of heparin. It has been known that beef and pork heparin induce HAAb; it has recently been shown that enoxaparin may induce HAAb.[22]

HAAb develop 5 to 14 days after the first exposure to heparin. However, one must be aware that thrombocytopenia and thrombosis may occur immediately upon response to heparin in a patient who developed HAAb during a previous exposure to heparin. Because of this, the platelet count should be determined before heparin administration and daily thereafter. HIT should be suspected in a patient receiving any form of heparin when any one of the following develop: thrombocytopenia (platelet count <100,000 mm^3 or a substantial decrease in the count), resistance to anticoagulation with heparin, or thrombohemorrhagic complications while receiving heparin. When HIT is suspected, all forms of heparin should be discontinued and the patient's plasma tested for the presence of HAAb. If HIT is confirmed, the platelet count should begin to rise and thromboembolic events should cease upon discontinuation of heparin. Discontinuation of heparin therapy is the key to improving morbidity and mortality; morbidity and mortality are as high as 61% and 23% when heparin is continued, but may be reduced to 22% and 12%, respectively, when the syndrome is recognized and heparin discontinued.[3] The mortality approaches 90% in patients with hemorrhagic (rather than thromboembolic) manifestations of HIT; fortunately, only 5% of patients with HIT have hemorrhagic complications. With heightened awareness of the syndrome and the prompt discontinuation of heparin, the morbidity and mortality may be reduced to rates approaching 0.[17]

Heparin-induced antibodies (usually IgG) are responsible for the platelet activation and aggregation noted in HIT syndrome. The antibodies appear to be specific for heparin because heparin may be used to remove the antibodies from plasma and because heparin excess can prevent platelet aggregation in HAAb plasmas.[19] Furthermore, patients with HIT have antibodies that react with heparin in a classic $F(ab^1)_2$ reaction.[23]

Drugs that inhibit platelet function or oral anticoagulants such as warfarin are appropriate substitutes for many patients with HIT. However, many of these patients continue to require therapy with an anticoagulant that allows rapid titrating of effects. Because LMWHs and heparinoids are as effective as UH in preventing thrombus formation, they have been used prophylactically for the prevention of deep venous thrombosis.[24,25] LMWH has a lower anti-

thrombin activity than UH and, therefore, a decreased incidence of bleeding complications.[25,26] Importantly, LMWH interacts differently with platelets than UH. Idiosyncratic platelet aggregation occurs less frequently with LMWH than with UH;[26] in high concentrations (equivalent to 100 U/ml UH), LMWH does not inhibit platelet aggregation with ristocetin as does UH; and LMWH inhibits collagen-induced platelet aggregation to a lesser degree than UH.[27]

Initially it was thought that these differences would lead to a lower incidence of HIT. LMWH was therefore used in several clinical trials in patients with HIT. These trials produced conflicting results; some investigators found that patients with HIT had reversal of their thrombocytopenia while receiving LMWH,[4-12] whereas others found that the thrombocytopenia persisted.[13-16] We have previously documented that the LMWHs mono-embolex NM and fragmin and the heparinoid Org 10172 have the ability to aggregate platelets in the presence of HAAb.[17] On the basis of these previous studies and on this study, which showed a high incidence of platelet aggregation in the presence of enoxaparin, we recommend that plasma from all patients with HIT who are being considered for treatment with LMWH undergo testing to ensure that the LMWH will not aggregate platelets in the presence of the patient's plasma.

As described, we have identified 83 patients with documented HIT whose plasma did not aggregate platelets in the presence of enoxaparin. Two of these patients required further heparin-like anticoagulation and safely received enoxaparin.

Thus although enoxaparin induces platelet aggregation in up to 34% of plasmas from patients with HIT, it may be safely used as a substitute for UH in those patients whose plasma does not aggregate platelets in the presence of enoxaparin.

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DISCUSSION

Dr. Thomas W. Wakefield (Ann Arbor, Mich.). The Missouri group is again on the forefront concerning the heparin-induced thrombocytopenia, or HIT, syndrome. In this study, 34% of positive plasma (as assessed by platelet aggregometry) in the presence of unfractionated heparin were positive for the low molecular weight heparin enoxaparin. Subdividing plasmas into positive categories, 88% of strongly positive plasmas with unfractionated heparin aggregated platelets in the presence of enoxaparin, whereas only 22% of limited positive plasmas with unfractionated heparin aggregated platelets in the presence of enoxaparin. Two patients with HIT syndrome who tested negative for enoxaparin safely received this low molecular weight heparin.

The in vitro method of testing for aggregation activity against the heparin in question is an excellent approach in the situation of HIT. I totally agree with the authors' conclusion that if the aggregation test against low molecular weight heparin is negative, one can safely use that heparin for anticoagulation. I have three short questions:

Have you had any experience using ^{14}C-serotonin testing for HIT? Many laboratories use this test for diagnosing HIT in preference to aggregometry, and I wonder if the use of ^{14}C-serotonin testing would improve accuracy even further?

Have you used low molecular weight heparins other than enoxaparin, and what is your experience with the heparinoid Org 10172? The incidence of HIT may be even lower with a low molecular weight heparin of very small size and an even greater antifactor Xa/antifactor IIa ratio than enoxaparin.

Finally, in day-to-day practice, when faced with the syndrome of HIT, which one of the heparin substitutes would be your first choice to use?

Dr. Milton Slocum. Your first question about ^{14}C-serotonin release testing for HIT: in our continuing effort to improve the accuracy of identifying plasmas that contain heparin-associated antiplatelet antibodies, we have evaluated many of the existing methods for determining the presence of heparin-associated antiplatelet antibodies and have found that the correlation between ^{14}C-serotonin release and platelet aggregometry is very good. In addition, we are developing an ELISA assay that may identify heparin-associated antiplatelet antibodies more accurately and more quickly.

Your next question concerns Organon 10172. Several years ago our laboratory published a paper in which the heparinoid and several low molecular weight heparins were studied the same way we studied enoxaparin in this paper. We found that the cross-reactivity to Org 10172 was less than that of enoxaparin (19.6%). We have not used Organon 10172 clinically.

Your last question is, "In day-to-day practice, what agent do we chose?" Our current practice is that every plasma that tests positive to unfractionated heparin, whether it be beef or pork, also automatically undergoes testing with enoxaparin. If the patient is judged to require a heparin-like agent for anticoagulation, we will use enoxaparin if the patient has tested negative to it. Otherwise, we block platelet function with aspirin and use limited amounts of heparin.

Dr. John D. Corson (Iowa City, Iowa). I was a little concerned about this epidemic of HIT in Missouri because we are not very far from you. Over what period of time where these 126 patients identified or were these samples sent to you by outside people?

Dr. Slocum. It is over about a 2 to 2½ year period, and a number of our samples are referred to us from other institutions.